CALIFORNIA'S STEM CELL AGENCY

CIRM

California Institute for Regenerative Medicine

MEMORANDUM

TO:	Members, Governing Board
FROM:	Gil Sambrano
RE:	Results of Appeals for RFA 13-05 Tools and Technology III
DATE:	March 13, 2015

BACKGROUND: At the last meeting of the Governing Board, we informed you that two applications were deferred from consideration in order to assess appeals made by each of the applicants. Both applicants appealed based on a material dispute of fact and both set forth adequate grounds for consideration. A subcommittee of the GWG was called together for each of the applicant appeals that included the chair of the GWG review, 3 scientific reviewers and 1 or 2 patient advocate members. The appeal request, which presented the applicants' rationale for disputing these facts, was presented to the GWG subcommittee. The GWG subcommittee was asked to consider whether clarification of the facts would have changed the reviewers' score and overall funding recommendation of the GWG.

RESULTS: In both cases, GWG reviewers agreed that clarification about the disputed facts did not impact their scores and would not have changed their recommendation. **Therefore, both applications are to be considered by the ICOC's Application Review Subcommittee with no change in the GWG recommendation.**

ADDITIONAL DETAILS:

Application RT3-07836

Score: *64* GWG Recommendation: *Not recommended for funding*

Summary of Appeal Review: The appeal is responding to specific criticism provided to the applicant in the review summary regarding the proposed experimental approach. Some review comments suggested that reviewers believed the technology would be applied to the differentiation of cardiomyocytes but the applicant points out that the proposal describes its use only for a cryopreservation step. The reviewers unanimously agreed that clarification on this specific point would not

have changed their overall recommendation. Two of the reviewers had been clear from the onset that the technology would be applied only to the cryopreservation steps and therefore, this did not impact their score. The third reviewer had not previously understood this point, but the reviewer did not consider this a significant component of his/her score. Furthermore, reviewers agreed that the milestone titles and the title of the proposal misrepresented the proposed activities and use of the technology.

Application RT3-07678

Score: 74 GWG Recommendation: *Tier 2*, *Moderate Quality or No Consensus*
CIRM Recommendation: *Fund*

Summary of Appeal Review: The appeal is responding to a specific criticism provided to the applicant in the review summary that "Reviewers would have preferred that the investigators propose testing the compound on additional differentiated cell types beyond the neuronal lineage to assess the breadth of its applicability". The applicants point to several instances in the application where they state the compound will be tested in varied cell types. The reviewers unanimously agreed that this specific point (i.e., testing the compound on additional cell types) was not a consideration or a significant element in determining their final score and recommendation. One reviewer had been unclear about the intent to study multiple cell types, but the reviewer did not consider it a deficiency, rather a recommendation.

Rationale for CIRM Funding Recommendation:
The proposal addresses the safety of human pluripotent stem cell (PSC) derived cells for transplantation; a bottleneck to clinical application of stem PSC derived cell therapies. Currently, there are no active grants in the CIRM portfolio that address this translational bottleneck and the small molecule approach is a potentially cost-effective way to address this safety bottleneck.

Like two other Tools and Technology applications in Tier 2 that were recommended for funding by CIRM and approved for funding by the ICOC's Application Review Subcommittee in January, this application had a median score of 75 and a majority of the voting members of the GWG scored the application in Tier 1.

TOTAL BUDGET RFA 1305

TIER 1	**$29,726,068**
TIER 2	**$4,995,058**

APP #	PROJECT TITLE	SCORE	Median	SD	Range Low	Range High	BUDGET	Number of Scores in Tier TIER 1	TIER 2	TIER 3	ICOC Action	Original GWG Tier
RT3-07692	Small molecule tools and scale-up technologies to expand human umbilical cord blood stem and progenitor cells for clinical and res	86	85	5	80	95	$1,416,600	15	0	0	Approved	Tier 1
RT3-07949	Embryonic stem cell-based generation of small animal models for assessing human cellular therapies	82	85	10	50	92	$1,499,400	14	0	1	Approved	Tier 1
RT3-07804	Injectable Macroporous Matrices to Enhance Stem Cell Engraftment and Survival	82	82	4	74	86	$1,452,708	13	1	0	Approved	Tier 1
RT3-07914	Skin-derived precursor cells for the treatment of enteric neuromuscular dysfunction	82	80	7	65	90	$1,818,751	14	1	0	Approved	Tier 1
RT3-07848	Site-specific gene editing in hematopoietic stem cells as an anti-HIV therapy	81	83	5	64	85	$1,500,624	14	1	0	Approved	Tier 1
RT3-07893	Optimizing the differentiation and expansion of microglial progenitors from human pluripotent stem cells for the study and treatmen	81	81	1	80	84	$1,147,596	15	0	0	Approved	Tier 1
RT3-07800	Engineered Biomaterials for Scalable Manufacturing and High Viability Implantation of hPSC-Derived Cells to Treat Neurodegenerati	77	80	7	55	82	$1,380,557	12	1	1	Approved	Tier 1
RT3-07683	Identification and isolation of transplantable human hematopoietic stem cells from pluripotent cell lines; two steps from primitive he	77	80	10	45	90	$1,452,708	11	2	1	Approved	Tier 1
RT3-07798	Advanced animal model for predictive preclinical testing of engineered cardiac autografts and allografts	77	80	22	10	98	$1,936,944	11	1	1	Approved	Tier 1
RT3-07948	Injectable Hydrogels for the Delivery, Maturation, and Engraftment of Clinically Relevant Numbers of Human Induced Pluripotent Ste	77	76	2	75	80	$1,452,708	15	0	0	Approved	Tier 1
RT3-07763	A suite of engineered human pluripotent stem cell lines to facilitate the generation of hematopoietic stem cells	76	80	10	45	83	$1,382,400	13	0	2	Approved	Tier 1
RT3-07655	User-friendly predictive molecular diagnostic assays for quality control of stem cell derivatives for transplantation and drug discove	76	79	8	60	90	$1,784,052	10	2	2	Approved	Tier 1
RT3-07879	Multimodal platform combining optical and ultrasonic technologies for in vivo nondestructive evaluation of engineered vascular tiss	76	75	10	50	90	$1,838,337	11	3	1	Approved	Tier 1
RT3-07907	Technologies to improve in vivo function of transplanted stem cells	75	75	10	50	86	$1,393,200	12	1	2	Approved	Tier 1
RT3-07796	A Chromatin Context Tool for Predicting iPS Lineage Predisposition and Tissue Graftability	75	75	4	64	82	$1,452,708	11	3	1	Approved	Tier 1
RT3-07616	Development of Relevant Pre-clinical Animal Model as a Tool to Evaluate Human Stem Cell-Derived Replacement Therapies for Motor	75	75	8	60	85	$1,308,711	10	3	2	Approved	Tier 1
RT3-07670	Development of a clinical-grade extracorporeal liver support system using human induced pluripotent stem cell-derived hepatic cells	75	75	9	50	95	$1,393,290	10	4	1	Approved	Tier 1
RT3-07678	A small molecule tool for reducing the malignant potential in reprogramming human iPSCs and ESCs	74	75	9	62	85	$1,341,161	9	1	5	Deferred	Tier 2
RT3-07899	Development of 3D Bioprinting Techniques using Human Embryonic Stem Cells Derived Cardiomyocytes for Cardiac Tissue Enginee	73	75	8	50	85	$1,368,517	9	4	1	Approved	Tier 2
RT3-07838	Development of a scalable, practical, and transferable GMP-compliant suspension culture-based differentiation process for cardiomy	72	75	9	50	87	$899,728	9	3	2	Approved	Tier 2
RT3-07981	Multi-modal technology for non-destructive characterization of bioengineered tissues	72	75	7	60	80	$1,846,529	9	2	3	Approved	Tier 2
RT3-07887	New materials and methods to instruct hematopoietic stem cell fate from human pluripotent precursors.	69	70	6	60	78	$1,373,966	4	6	5	Not Approved	Tier 2
RT3-07808	A novel experimental procedure to generate large-scale cultures of human multipotent progenitors	66	65	6	55	75	$1,161,000	3	6	6	Not Approved	Tier 2
RT3-07832	Survival and Function of Individual Stem Cells Measured Longitudinally in Small Animal Model In Vivo	66	64	5	60	75	$1,118,931	2	5	8	Not Approved	Tier 2
RT3-07836	Multivalent growth factor conjugates for improved efficiency of stem cell expansion and differentiation	64	63	5	60	75	$1,313,489	1	2	11	Deferred	Tier 3
RT3-07974	MRI reporters to noninvasively image long-term stem cell engraftment in large animal spinal cord injury model	64	61	7	50	78	$1,857,600	2	5	8	Not Approved	Tier 3
RT3-07632	Tools to harness in vivo signals for the generation of definitive hematopoiesis from human pluripotent stem cells	63	64	5	50	75	$1,373,180	1	1	13	Not Approved	Tier 3
RT3-07870	Recapitulating the 3D Microenvironment for Directing Vascular Fate	62	63	5	50	74	$1,064,703	0	1	13	Not Approved	Tier 3
RT3-07633	Bioengineering personalized functional lungs using induced pluripotent stem cell technology	61	64	10	45	80	$1,363,544	1	1	12	Not Approved	Tier 3
RT3-07880	Mitochondrial genome editing tools for the generation of novel animal and stem cell models	61	60	8	50	77	$1,743,120	1	2	12	Not Approved	Tier 3
RT3-07859	3D Bioprinting for Stem Cell Delivery	61	60	4	50	64	$2,182,176	0	0	14	Not Approved	Tier 3
RT3-07662	Engineering instantly integrated vascularized tissues for enhanced engraftment and tissue regeneration	<60					$1,440,426	1	0	12	Not Approved	Tier 3
RT3-07756	Delivery of stem cells for muscular dystrophy	<60					$1,735,180	0	0	15	Not Approved	Tier 3
RT3-07864	The generation and expansion of fully functional human hematopoietic stem cells by cellular delivery of RUNX1a transcription factor	<60					$1,857,599	0	0	15	Not Approved	Tier 3
RT3-07805	A scaffolding system to enhance lineage-specific differentiation of pluripotent stem cells by on-demand mechanomodulation of the c	<60					$1,060,025	0	0	14	Not Approved	Tier 3
RT3-07738	High-fidelity genome engineering to treat genetic disease	<60					$1,708,560	2	1	12	Not Approved	Tier 3
RT3-07898	Skeletal Muscle Regeneration by Direct Cellular Reprogramming of Human Fibroblasts to Satellite Cells with Myogenic and Cell-pene	<60					$1,570,500	0	0	14	Not Approved	Tier 3
RT3-07813	Magneto-endosymbionts; in vivo translational tools for stem cell imaging and ablation.	<60					$900,000	0	0	15	Not Approved	Tier 3
RT3-07883	Developing novel genetic neurological disease monkey models with and without stem cell transplantation	<60					$1,152,000	0	0	15	Not Approved	Tier 3
RT3-07851	Development of an optimized stem-cell-seeded xenogeneic extracellular matrix construct and delivery system for cardiac repair follo	<60					$1,809,305	0	0	15	Not Approved	Tier 3
RT3-07901	Label-free analysis and purification of cell-based therapies for cost-effective regenerative medicine	<60					$1,237,352	0	0	15	Not Approved	Tier 3
RT3-07975	A comprehensive microfluidic platform for the production of stem cell micro-beads for therapeutic transplantation	<60					$900,000	0	0	15	Not Approved	Tier 3
RT3-07841	Advancing Stem Cell Replacement Therapies through Precision Single-Cell Profiling	<60					$1,327,648	3	0	11	Not Approved	Tier 3
RT3-07962	A large animal model of mucopolysaccharidosis I for stem cell therapy development.	<60					$1,669,272	0	0	15	Not Approved	Tier 3
RT3-07855	Neuronal Precursor Cell Therapy in Large Animals: Delivery, Dosing, Safety, and Efficacy	<60					$1,651,680	0	0	15	Not Approved	Tier 3
RT3-07891	Enhancing thymic epithelium differentiation with three dimensional matrices and small molecule libraries	<60					$1,429,200	0	0	15	Not Approved	Tier 3
RT3-07750	Development of Clinical Tools for Predicting and Evaluating Immune Responses to Regenerative Cellular Therapies	<60					$1,374,020	0	0	15	Not Approved	Tier 3
RT3-07881	iPSC-based Bioartificial Liver device	<60					$1,934,352	0	0	13	Not Approved	Tier 3
RT3-07965	Optimizing safety and efficacy of transgenic human induced pluripotent stem cell-based personalized cellular therapeutics	<60					$1,345,730	0	0	15	Not Approved	Tier 3
RT3-07990	Joint surface regeneration: Deliver stem cells and control their fate with novel intelligent clinical grade biomimetic materials	<60					$1,025,839	0	0	15	Not Approved	Tier 3
RT3-07900	Bioactive thermo-reversible polymers as adjunctive therapy to stem cell treatment of heart failure	<60					$1,904,077	0	0	15	Not Approved	Tier 3

REVIEW REPORT FOR CIRM RFA 13-05 TOOLS AND TECHNOLOGIES III AWARDS

RT3-07678: A small molecule tool for reducing the malignant potential in reprogramming human iPSCs and ESCs

GWG Recommendation: Tier 2
Final Score: 74

Public Abstract (provided by applicant)

This research project aims to solve a key bottleneck in the use of differentiated human embryonic stem cells and induced pluripotent stem cells for the regeneration and replacement of diseased or damaged tissues. This bottleneck is the potential of unintended transplants containing failed-to-differentiate stem cells developing into benign growths called teratomas, or worse, malignant teratocarcinomas. It is essential to overcome this safety concern before stem cell-derived therapies can become acceptable for human use. Stem cells and cancer cells have many common properties. Both can replenish themselves indefinitely, and can potentially grow in different parts of the body. Before they are administered to patients, stem cells must be forced in the laboratory to turn into more mature cells that are programmed to become neurons, heart cells, beta cells of the pancreas, and other differentiated cell types. The mature cells, unlike the stem cells, do not grow indefinitely, but rather can replace a specific function that is defective in disease. We have identified a specific small molecule tool that selectively kills pluripotent stem cells but does not damage differentiated lineage cells. We will investigate the mechanism of action of the tool and test the tool for specificity in a variety of pluripotent stem cells and their differentiated lineages. The end goal is to develop a technology that will minimize the potential of developing unexpected tumors from stem cell therapies.

Statement of Benefit to California (provided by applicant)

Our proposal benefits California by adding new essential knowledge on mitochondrial mechanisms that control human pluripotent stem cell (hPSC) function to support the taxpayers' commitment to personalized cell therapies. This work builds on highly successful CIRM Seed & Basic Biology I awards. CIRM funds to date resulted in 20+ publications and training of 14 individuals including post-docs, graduate students, undergraduates, and CIRM Bridges to Stem Cell Biology program trainees, some of whom have entered the California workforce. Here we have identified a small molecule modulator of a mitochondrial redox protein that selectively kills pluripotent stem cells but not their differentiated lineages. Because contamination by hPSCs in transplanted donor cell pools is a key concern for regenerative cell therapies, there is a critical need to develop methods for reproducibly eliminating potentially cancerous cells. Our small

molecule is an exciting candidate tool and will be characterized extensively. Our ongoing work underpins therapy development in California's major academic centers and will provide data for many of California's biotechnology companies in the growing stem cell industry, whose success will propel hiring and increased economic prosperity for the state. With success, tangible health and economic impact on California, its academic institutions and companies, and the rest of the nation will be achieved as California leads the way forward with personalized medicine.

Review Summary

Proposal Synopsis
The applicant proposes to develop a method to selectively eliminate undifferentiated human pluripotent stem cells (hPSCs) in cell therapy transplants. To accomplish this goal the applicant has identified a small molecular tool that recognizes and removes hPSCs, but does not affect differentiated cells. The proposal aims to investigate the mechanism of action of this molecule and to test it for specificity on varied populations of human embryonic stem cells, induced pluripotent stem cells, and their differentiated progeny. Their ultimate goal is to develop a technology that will minimize the potential of tumor formation with pluripotent stem cell-derived therapies.

Significance and Rationale
- The applicant proposes to eliminate the residual undifferentiated pluripotent cells from the population of differentiated cells by using a small molecular probe. If successful, and able to demonstrate the removal of any residual probe in the screened transplants, this would be a significant advancement in human stem cell therapy.

- Reviewers acknowledged that the rationale was supported by convincing preliminary data provided by the applicant. A concern was expressed that the applicant did not demonstrate the advantages of this approach over other methodologies.

Feasibility and Experimental Design
- The applicant will perform experiments on various undifferentiated and differentiated stem cell lines to determine the effective doses of the compound, as well as a potential mechanism of action. The experiments are logical and well thought out. The preliminary data that is provided supports the experimental design and approach.

- Reviewers would have preferred that the investigators propose testing the compound on additional differentiated cell types beyond the neuronal lineage to assess the breadth of its applicability.

- A concern was raised that potential downstream effects of the small molecule on the function of differentiated cells need to be assessed to know if this could be used clinically.

Qualifications of PI and Team

- The principal investigator and collaborators are well qualified to conduct the research with appropriate institutional commitment and excellent resources.

- The collaborators are well established investigators in stem cell biology and small molecule chemistry, which improves the outcome for success on the project.

Responsiveness

- The proposal is responsive to the RFA in that it addresses a significant bottleneck in enabling the safe use of pluripotent stem cells in regenerative medicine applications.

- Human ESCs and iPSCs will be used in this proposal. If successful, the results and techniques can be used throughout the stem cell community.

- The reviewers had some reservations as to the direct translation of the tool /technique for clinical applications.

REVIEW REPORT FOR CIRM RFA 13-05 TOOLS AND TECHNOLOGIES III AWARDS

RT3-07836: Multivalent growth factor conjugates for improved efficiency of stem cell expansion and differentiation

GWG Recommendation: Not recommended for Funding
Final Score: 64

Public Abstract (provided by applicant)

Biomanufacturing of stem cell products is fundamentally different from the manufacturing of vaccines and biologics, since in stem cell biomanufacturing the cells are the product. Most of the CIRM-funded research to date has focused on the upstream steps of the biomanufacturing processes such as stem cell isolation, culture conditions for cell maintenance and expansion, and this productive research has yielded viable solutions, but at significant per-patient costs. For example, we are part of a CIRM-sponsored collaboration to develop a stem cell-based engineered heart tissue, which will be used to for treatment after an infarct. For this device to be effective, approximately one billion stem cells are required to achieve sufficient cellularity in the graft. A substantial component of the overall cost for this type of stem cell treatment is due to the chemical reagents that are used to direct the stem cell to replicate and to differentiate into the specialized cell types that can provide effective treatment. My laboratory has developed methods to engineering these reagents to increase their potency. As a result, we can reduce the amount of these reagents that are required for stem-cell bio manufacturing to as little as 10% compared to the amounts that are currently required. Therefore, we anticipate the findings of this project should dramatically reduce the costs associated with stem cell therapy and to improve the access to these therapies for patients who need them.

Statement of Benefit to California (provided by applicant)

Tens of thousands of Californians suffer from diseases that CIRM researchers are currently developing stem-cell based therapies as effective treatment options. Despite the clinical successes achieved using stem cells, access to these new therapies are currently limited by the high cost associated with stem cell biomanufacturing. In this project, we will specifically address the costs associated with the growth factors used to promote stem cell expansion, differentiation and functional recovery after cryopreservation. By engineering growth factor conjugates that are approximately an order of magnitude more potent that unconjugated growth factors, we will dramatically reduce the amount of these reagents that are required, as well as their associated costs. Therefore, we will lower a critical price-barrier that currently exists and currently limits the wide-spread clinical use of emerging stem cell therapy breakthroughs.

Review Summary

Proposal Synopsis
This proposal aims to address two bottlenecks in the development of stem cell-based therapeutics: the large expense of manufacturing stem cell products at a clinically relevant scale; and the decreases in functional capacity that can occur in these products after cryopreservation. To meet these objectives, the applicant proposes to investigate the impact of growth factor (GF) conjugates on key steps in the growth and differentiation of human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs). He/she argues that such conjugates can be engineered to exhibit equivalent bioactivities as their typical, unconjugated counterparts at much lower concentrations, thereby reducing the amount of GF needed for the various stages of cell processing and dramatically lowering the costs associated with manufacturing hESCs and iPSCs for cell-based therapies. Research objectives are to 1) develop and characterize a specific GF conjugate system for expanding hESCs and iPSCs in suspension culture; and 2) evaluate the cost-effectiveness of using GF conjugates to differentiate hESCs and iPSCs to cardiomyocytes, a critical cell type that is lost after heart attack.

Significance and Rationale
- Developing more efficient and cost effective methods for generation and expansion of hESCs and iPSCs is highly significant. If successful as envisioned, the project could have major impact.

- The rationale for improving cardiomyocyte survival after cryopreservation with the proposed GF conjugate is not well supported by the preliminary data. Moreover, reviewers were skeptical that varying GF concentrations would lead to mature cardiomyocytes.

- Application of the proposed technology to a suspension cell culture system is novel.

- Concerns were raised that extending the conjugate technology to a cardiac differentiation procedure that requires multiple media components or exchange steps could render the overall process quite expensive for further clinical applications.

Feasibility and Experimental Design
- While there were strong preliminary data supporting the utility of GF conjugates in other contexts, reviewers were doubtful that this information could be directly extrapolated to the proposed system for cardiac differentiation and thus questioned the overall feasibility of Aim 2.

- The proposed time frame is reasonable, and the investigators have ready access to needed reagents, protocols, and an established large scale manufacturing technology.

- Reviewers suggested that if the proposed technology is to be widely useful, it should be tested with additional systems/protocols for producing cardiomyocytes.

Qualifications of PI and Team

- The PI is a renowned, established investigator with a successful track record in the areas of biomaterials, stem cell differentiation and the cardiac lineage.

- The assembled team of collaborators provides outstanding, complementary expertise.

Responsiveness

- The proposal aligns with an RFA objective aimed towards reducing the costs of human stem cell manufacturing processes.

- Reviewers perceived the overall proposal as a series of small projects that were pieced together to create a responsive proposal.